Therapeutic Opportunities To Target Tumor Initiating Cells in Solid Tumors

Grant Award Details

Therapeutic Opportunities To Target Tumor Initiating Cells in Solid Tumors

Grant Type: Disease Team Research I

Grant Number: DR1-01477

Project Objective: The goal of this project was to file an IND for a small molecule therapeutic that will target solid tumor cancer stem cells and eliminate them.

Investigator:

Name:	Dennis Slamon
Institution:	University of California, Los Angeles
Type:	PI

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Name:	Garry Nolan
Institution:	Stanford University
Type:	Co-PI

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Name:	Michael Press
Institution:	University of Southern California
Type:	Co-PI

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Name:	Tak Mak
Institution:	University Health Network
Type:	Partner-PI

Disease Focus: Solid Tumor, Cancer

Collaborative Funder: Canada

Human Stem Cell Use: Cancer Stem Cell

Award Value: $19,979,660

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: Year 4

View Report

Reporting Period: NCE (Year 5)

View Report

Grant Application Details

Application Title: THERAPEUTIC OPPORTUNITIES TO TARGET TUMOR INITIATING CELLS IN SOLID TUMORS

Public Abstract: Cancer is a major cause of human death worldwide. The vast majority of cancer patients suffer from solid tumors whose growth destroys vital organs. We propose to develop novel therapeutic drugs that target solid tumors affecting the brain, colon and ovaries. These cancers account for a significant proportion of currently intractable solid malignancies.

Scientists have made great strides in understanding the molecular and cellular changes that cause cancer but the approval of new therapeutics that can specifically kill cancer cells has lagged behind. This disparity suggests that there must be critical bottlenecks impeding the process of turning a basic research discovery into a finished anti-cancer drug. Research over the past decade has given rise to the idea that one of these bottlenecks may be caused by the existence of cancer stem cells. According to the cancer stem cell hypothesis, there is a minor population of cancer stem cells that drives the growth of the entire tumor. However, cancer stem cells are very rare and hard to identify. Technical innovations have recently allowed the identification, isolation and growth of these cells in the laboratory, and it has become clear that they have properties that are distinct from both the bulk of tumor cells and the cancer cell lines usually used to test anticancer drug candidates. Furthermore, in the lab, cancer stem cells are resistant to the chemotherapy and radiation treatments used to kill most tumor cells. In a patient, cancer stem cells may not be killed by standard drugs and may eventually regrow the tumor, causing a cancer to relapse or spread. Thus, a drug that specifically targets cancer stem cells could dramatically improve the chances of treatment success.

Our team is one of the few in the world that can identify cancer stem cells in brain, colon and ovarian tumors. Furthermore, we have developed assays that can accurately test the effectiveness of drug candidates in killing these cells. Our preliminary data suggest that our lead drug candidates can inhibit the growth of cancer stem cells in culture and block tumor initiation in animal models. Importantly, our drug candidates appear to work through mechanisms that are different from those employed by current chemotherapeutics, meaning that our drugs represent a fresh and potentially very effective approach to cancer treatment. Over the next several years, we propose to complete our development and preclinical studies of these drugs so that testing in cancer patients can begin.

Statement of Benefit to California:	Our proposal may benefit the state of California in four important ways. First, solid tumors cause significant morbidity and mortality. We propose to develop 2-3 Investigational New Drugs (INDs) to treat colon, brain and ovarian tumors, which are often difficult to treat with conventional therapies and are associated with poor prognoses. Thus, the proposed INDs should lead to a decreased burden on the California health system. The second benefit arises from our novel approach to drug development, a route that other researchers may emulate. Most targeted cancer drugs fail in clinical trials, despite our growing knowledge of the molecular and cellular causes of cancer. These failures indicate that there are rate-limiting factors in the way basic research is currently translated to cancer drug discovery and development. One such factor may be related to a major new hypothesis in tumorigenesis, which states that a minor population of cancer initiating cells (CICs) drives bulk tumor growth. These CICs appear to survive existing therapies that kill most tumor cells, and so can go on to initiate relapses and metastases. A second rate-limiting factor may be the heterogeneity that exists both among and within different tumor types. Both of these "bottleneck" factors can be obviated by the molecular characterization and comparison of CICs and bulk tumor cells. Knowing the features that distinguish CICs from bulk tumor cells will facilitate a targeted drug development plan that optimizes chances for clinical success. We have devised such a strategy based on the integration of solutions to these limiting factors into a state-of-the-art drug discovery platform. This strategy may provide a foundation for the rapid extension of our approach to the treatment of other solid tumors. The third benefit is the linking of CIC identification to clinical outcome. The ability to isolate and propagate CICs from solid tumors is a recent innovation. We will perform a thorough genetic examination of the alterations in these cells that lead to oncogenesis. Because we intend to carry out this work in parallel with the characterization of tumor samples from patients with documented clinical outcomes, we will be able to correlate the nature of particular CICs with similarities/differences among human tumors in a way that identifies features statistically linked to poor outcomes. This information will allow the selection and validation of additional drugs so that a pipeline of ever more refined compounds is established even if initial attempts fail in the clinic. The fourth benefit falls directly in line with the focus of California's robust biotechnology industry on drugs to address unmet medical needs. Our data and methods will be published and readily available, and so can be applied by existing and emerging biotech companies. Great advances in novel targeted therapeutics to treat solid tumors should be realized, expanding the drug development expertise of the state.